› CASE STUDY

VERISTAT

Uncharted Waters in Gene Therapy

Groundbreaking Work Leads to First Gene Therapy Ever Approved in Europe

Background: Setting a New Standard for the Industry

Veristat was brought in to create and manage a full development program for a gene therapy for a very rare inherited disorder. The work involved charting the course in completely uncharted waters – our team had to create industry best practices that didn't exist before, anywhere. With no classic route to market, Veristat's experts wrote the map on patient recruitment, regulatory and health agency engagement, biometrics management, natural history studies and the Central Site Model. There were unique, first-of-their-kind challenges every step of the way. From Phase I rescue to long-term follow up, our team's expertise and dedication helped the client cross the finish line with the first gene therapy ever to be approved in Europe.

Study Demographics

Indication:

Reverse Lipoprotein Lipase Deficiency

Full Service from Phase I to Long-Term Follow Up

Primary Services Provided:

- Regulatory Affairs
- Project Management
- Clinical Monitoring
- Data Management
- Statistics
- Medical Writing
- Medical Monitoring
- Medical Affairs

SOLUTION

Creating a development roadmap for uncharted territory

Veristat was initially brought in to rescue a Phase I study. Based on our team's superior knowledge and execution, our involvement then expanded into a full program. Many critical challenges presented themselves throughout the duration of the trial. One key challenge was that very few people globally are known to have reverse lipoprotein lipase deficiency, which is prevalent only in people of Dutch descent. This low disease prevalence prompted the necessity to revisit our entire clinical trial approach while keeping patients at the center.

Patient recruitment

First in human studies were conducted in the Netherlands and had already made use of most of the people suffering from the disease globally. Additionally, the gene therapy was not a treatment but a cure – and once patients are cured, they leave the study, meaning even fewer subjects at hand. Patient recruitment, then, was the first major challenge and a dealbreaker. Veristat's experts designed a strategy to "hunt" for subjects, scanning publications on the disease to find incidences around the globe. Given the disease's issue of a missing lipase enzyme, patients tend to get pancreatitis and suffer from depression – clues that helped our team in the search. Veristat was able to identify some patients in South Africa, which has a high population of people with Dutch ancestry.

Data management

There were a number of challenges that impacted how data was evaluated and managed that included:

- The use of two protocols and lengthy CRFs. The CRFs contained several pages with particularly unusual parameters on family history of LPL deficiency and chicken pox, assessment of pancreatic calcification, local anaesthetist review, multiple symptoms assessments (plasma lactescence, xanthoma, lipemia retinalis, etc.), dietary counsel, QPCR of bodily fluids and fractionated semen, and more.
- The protocols, CRFs, questionnaires and diary card information needed to be amalgamated into one database which required our creative ingenuity in the design of the database.
- Extra care needed to be taken during the time-consuming data entry process with no opportunity to create data queries. If not managed properly using the utmost attention to detail, data accuracy and completeness would have suffered.
- There was a sizable amount of electronic data from different vendors which required numerous data transfer types and entry and cleaning from diary card data. Organization and oversight of this intricate process was a necessity.

Statistics

Population scarcity was a difficulty from the outset even for this early phase trial. Despite our creative approaches to recruit patients, five was the total amount enrolled. A modified trial design was warranted which used statistical techniques to maximize all data sources:

- The trial design evolved from comparative to open label to address the low sample size.
- Data was visually presented to enable ease of understanding of possible trends and potential efficacy benefits.
- A novel statistical solution was established which used the presentation of photographic retinal assessments and correlation methods to the repeated clinically

applied assessments of the photographs versus changes in outcomes over time. This allowed for confirmation of data validity and consistency while taking into account subjective clinical assessments.

Due to the condition's rare disease status, regulatory authorities required an adaptive statistical design model in which rapid submission of data — from IA1 to IA2 to final reporting of follow up — was mandated. Timing was critical as the Veristat statistics team needed to expediently present the results while ensuring the utmost quality. To illustrate the significance of the compressed timeline: the IA1 monitoring cut off was October 31, 2009 with the data needing to be cleaned, locked, and reported in less than sixty days.

Natural history

Veristat designed a natural history study that served as a historical control arm to overcome the lack of study subjects, looking to Canada, where a small population of people with the disorder were found in Quebec. This was traced to one man with an incredibly rare "spontaneous mutation" of the disorder in Toulouse, France who later moved to Quebec. There were not enough patients in Canada for a randomized clinical study, so our experts created a historical control arm instead, using robust data available from childhood to time of treatment. This meant having to collect data in person from centers all over Canada in very inhospitable winter weather.

Central site model

The process for delivering the novel gene therapy was highly complex. In order to reduce the potential for variation, we developed a central site model for treatment. Additionally, there was a specialist challenge component to the efficacy analysis; given this, we used the central site model for this assessment as well. Patients who were recruited from the Centres in Toronto and throughout Quebec were sent to the Centre Sites in Chicoutimi for treatment and to the Sherbrook facility for the challenge. Patients subsequently returned to their recruiting site for follow up.

Challenge arm

To prove that the gene therapy did indeed work, the Veristat team set up a unique challenge arm – feeding patients lipids in the form of a special milkshake to see how they responded after gene therapy treatment. This required identifying and training physicians who could formulate the right milkshake, deliver it the right way and deal with the patient if anything went wrong.

Regulatory

As with the rest of the program, regulatory strategy and interaction followed an iterative process every step of the way. Veristat's specialists had more expertise on the subject than regulators, who weren't at the forefront of gene therapy.

- Health Canada: Our team worked to educate regulators on the product and trial, and how we could address the body's concerns from the very beginning.
- European Medicines Agency (EMA): For any new therapy, the first product is the biggest hurdle, and Veristat created a process where there was no process. The level of rigor and quality was much higher than for an "average" product.
- Committee for Advanced Therapies (CAT), Europe: The regulatory meeting featured much tougher questions – it would take an expert to have any answers at all, let alone the right answers. Pre-approval inspections were also a much higher burden for our team.
- Medicines and Healthcare Products Regulatory Agency (MHRA), UK and the Turkish Medicines and Medical Devices Agency (TMMDA): We worked closely with MHRA and Turkish Competent Authorities as part of their implementation of the Advanced therapy.

IMPACT

First gene therapy approved in the EU (and only the 7th to go before the CAT)

- The approval was a pivotal moment in medicine – the first time anyone showed that a gene therapy could even be approved. The net result was more investment and interest in the potential of gene therapy to help patients in dire need.
- There are always unique issues to overcome in gene therapy, but Veristat's passion, global expertise and outside-the-box, pioneering thinking brought the client to the finish line and proved we can find a solution for every situation.

- Our team became the expert consultant for gene therapy around the globe, called on by both drug developers and regulatory and healthcare bodies.
- What's best for patients is best for payers – we all want to cure a disease if we can.

ABOUT VERISTAT

The cell and gene therapy partner of choice

We understand how high the stakes are with your cell and gene therapy program. We know that nothing is standard about study design, study conduct or regulatory process in this specialized area. Veristat has successfully supported more than 100 cell and gene therapy projects, with a global team of scientific experts who are adept at strategy and execution across the clinical development pathway. Learn more about Veristat and how we can assist you with your cell or gene therapy trial development, execution, and regulatory submission preparation.

Contact Veristat Today

Learn more about our cell and gene therapy expertise.

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